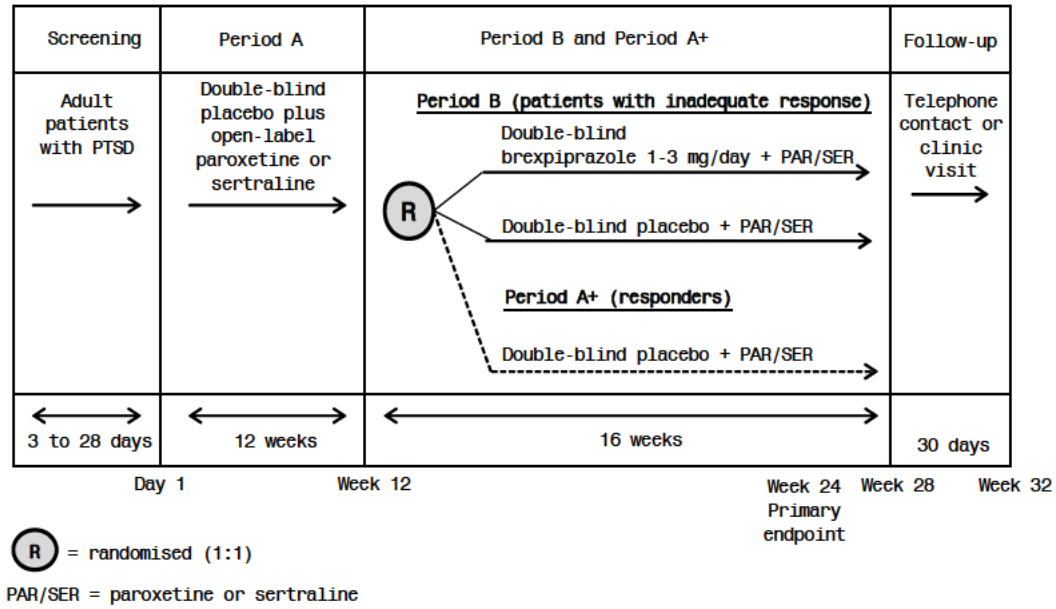
Synopsis – Study 14865A

Study Title Interventional, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study of brexpiprazole as adjunctive treatment to paroxetine or sertraline in adult patients suffering from post-traumatic stress disorder (PTSD)
Investigators 72 principal investigators at 72 sites in 11 countries *Signatory investigator* – [redacted]
Study Sites 72 sites – 3 in Argentina, 1 in Estonia, 6 in Finland, 5 in France, 5 in Italy, 4 in Mexico, 5 in Poland, 6 in Serbia, 9 in South Africa, 3 in Sweden, and 25 in the United States
Publications None (as of the date of this report)
Study Period *First patient first visit* – 12 December 2013 (the date when the first *Informed Consent Form* was signed) *Study terminated* – 27 August 2015 *Last patient last visit* – 30 October 2015 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to evaluate the efficacy of brexpiprazole 1 to 3 mg/day as adjunctive treatment to paroxetine or sertraline on PTSD symptoms. • *Secondary objectives*: – to evaluate the efficacy of brexpiprazole 1 to 3 mg/day on: • clinical global impression • sleep quality • depressive and anxiety symptoms • functioning • health-related quality of life • *Safety objective*: – to evaluate the safety and tolerability of brexpiprazole 1 to 3 mg/day

Study Methodology

- This was an interventional, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study.
- Patients were recruited from the investigator's own patient population, via advertisement (if allowed in the country), or via referrals.
- The study consisted of a screening period (lasting from 3 to 28 days), a blinded treatment period (Weeks 0 to 28), and a safety follow-up period (Weeks 28 to 32).
- The blinded treatment period consisted of Periods A, B, and A+:
  - Period A: the patients received 12 weeks of open-label treatment with either paroxetine or sertraline, at the discretion of the investigator, together with double-blind placebo treatment. The dose of paroxetine was increased from 20mg/day to 30mg/day during the first week. Further dose increase to 40mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 20 or 30 mg/day until the Week 8 Visit in steps of 10mg/day per week. The dose of sertraline was increased from 50mg/day to 150mg/day during the first 2 weeks. Further dose increase to 200mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 100, 150, or 200 mg/day until the Week 8 Visit in steps of 50mg/day per week. After 12 weeks of treatment, the patients with inadequate response to sertraline or paroxetine were randomised 1:1 to receive adjuntive treatment with brexpiprazole or placebo and entered Period B. Inadequate response was defined as a Clinician-Administered PTSD Scale Part 2 (CAPS-2) total score ≥65 at the Week 8 and 12 visits in Period A. The visit at which the patient was randomised was blinded to both the patient and the investigator. The patients who had responded to sertraline or paroxetine in Period A continued in Period A+.
  - Period B: the patients received 16 weeks of double-blind treatment with 1 to 3mg/day brexpiprazole or placebo in addition to the open-label paroxetine or sertraline treatment they received in Period A. The dose of brexpiprazole was 1mg/day for one week, followed by 2mg/day for 3 weeks. Thereafter, the dose was flexible and could be adjusted from 1 to 3mg/day. No dose adjustments of paroxetine or sertraline were allowed in Period B.
  - Period A+: the patients continued with the same treatment they received in Period A and followed the same assessment schedule as the patients in Period B. No dose adjustments of paroxetine or sertraline were allowed in Period A+.
- Study design is presented below:



Study Methodology (continued)

- Efficacy and safety data were collected at regular intervals throughout the study.
- A safety-follow-up visit was scheduled 4 weeks after completion/withdrawal from the study.
- The study was terminated early due to challenges with patient eligibility; the decision to terminate was not based on any safety concerns. The affected patients were withdrawn at their next scheduled visit.

Number of Patients Planned

592 patients were planned for enrolment in order to randomise 296 patients: 148 in the brexpiprazole group and 148 in the placebo group.

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of PTSD according to DSM-IV-TR™ criteria (confirmed using the Mini International Neuropsychiatric Interview [MINI]), who:

- had a CAPS-2 total score ≥70 at the Screening Visit and at the Baseline A Visit
- were ≥18 and ≤65 years of age
- had reported duration of PTSD ≥3 months
- had the index traumatic event that led to development of PTSD ≤15 years prior to screening

Patients were randomised and entered Period B, if they:

- had a CAPS-2 total score ≥65 at the Week 8 and 12 Visits in Period A

Investigational Medicinal Products, Doses and Modes of Administration, Batch Numbers

Brexpiprazole – 1, 2, or 3 mg/day; tablets, orally; batch Nos. 14D71A001C (1 mg), 13A97A001 (1 mg), 13E92A002 (2 mg), 13A98A002 (2 mg), 13E96A003 (3 mg), and 13A99A003 (3 mg)

Reference Therapy, Doses and Mode of Administration, Batch Numbers

Placebo – tablets, orally; batch Nos. 13A92P005A and 14C97P005B

Non-investigational Medicinal Products, Doses and Modes of Administration, Batch Numbers

Paroxetine – 20 or 30 mg/day; tablets, orally; batch Nos. PA0213008-A (20 mg), 155130020A (20 mg), PA0312001-A (30 mg), PA0313003-B (30 mg), and 156130006A (30 mg)

Sertraline – 50 or 100 mg/day; tablets, orally; batch Nos. SESB13005A (50 mg), XT5013015-A (50 mg), XT5014063-A (50 mg), SESC13043A (100 mg), XT1013019-A (100 mg), and XT1014037-A (100 mg)

Duration of Treatment

Brexpiprazole as adjunct treatment to sertraline or paroxetine for 16 weeks.

Efficacy Assessments

- CAPS-2
- Montgomery and Åsberg Depression Rating Scale (MADRS)
- Clinical Global Impression – Severity of Illness (CGI-S)
- Pittsburgh Sleep Quality Index (PSQI)
- Sheehan Disability Scale (SDS)
- Hospital Anxiety and Depression Scale (HADS)
- PTSD Checklist - Civilian Version (PCL-C)
- World Health Organization Brief Quality-of-Life Assessment (WHOQOL-BREF)

Pharmacokinetic Assessments

- Plasma concentrations of paroxetine, sertraline, brexpiprazole, and brexpiprazole's major metabolite DM-3411
- Genotyping for CYP2D6

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/BMI (body mass index)/waist circumference, electrocardiograms (ECGs), and physical examinations
- Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Rating Scale For Drug-induced Akathisia (BARS)
- Modified Simpson Angus Scale (mSAS)

Endpoints

- *Primary endpoint*:
  - PTSD symptoms:
    - change from randomisation to Week 24 in CAPS-2 total score
- *Key secondary endpoints*:
  - global clinical impression:
    - change from randomisation to Week 24 in CGI-S score
  - functioning:
    - change from randomisation to Week 24 in SDS score
- Further efficacy endpoints in this study are presented in Addendum I of the study protocol
- *Safety endpoints*:
  - adverse events
  - absolute values and changes from randomisation in clinical safety laboratory tests, vital signs, weight, BMI, waist circumference, and ECG parameters
  - potentially clinically significant clinical safety laboratory test values, vital signs, weight, BMI, waist circumference and ECG parameter values
  - physical examinations
  - eC-SSRS and categorised based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA)
  - Change from randomisation in AIMS total score, BARS Global Clinical Assessment of Akathisia score (Item 4 of the BARS), and mSAS total scores

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated Period A set* (APTSPA) – all patients who took at least one dose of paroxetine/sertraline and/or placebo in the study
  - *all-patients-treated set* (APTS) – all randomised patients who took at least one dose of double-blind IMP after randomisation
  - *Full-analysis set* (FAS) – all patients in the APTS who had an assessment at randomisation and an assessment after randomisation of the CAPS-2 total score
  - *all-patients-treated Period A+ set* (APTSPA+) – all patients who completed Period A, but were not randomised in Period B and had at least one efficacy or safety assessment in Period A+
- The limited number of randomised patients resulted in insufficient data for any meaningful efficacy analyses. For completeness, descriptive statistics of the absolute values for the CAPS-2 total score and CGI-S score are presented by visit for the APTSPA (Period A) and FAS (Period B).
- The safety was summarised as follows: Period B safety data were presented for APTS, Period A and Period A+ safety data were presented when relevant for APTSPA and APTSPA+.
- Disposition and withdrawals were presented for the APTSPA (for all periods and Period A), APTS (Period B), and APTSPA+ (Period A+). Demographics were presented for the APTSPA, APTS, and APTSPA+ and baseline characteristics (including PTSD-related trauma history and onset and diagnosis of PTSD) were presented for the APTSPA and APTS.
- Exposure was presented for the APTSPA (Period A), APTS (Period B), and APTSPA+ (Period A+) and IMP compliance was presented for the APTS (Period B).
- Recent and concomitant medication was classified according to the start and stop time of IMP (discontinued prior to first dose of randomised IMP; continued after first dose of randomised IMP; and started at or after first dose of randomised IMP) and summarised by anatomical therapeutic chemical (ATC) code and generic drug name for patients in the APTS.
- The incidences of adverse events for the patients in the APTSPA (Period A) and APTSPA+ (Period A+) and treatment-emergent adverse events (TEAEs) for the APTS (Period B) were tabulated by primary system organ class (SOC) and preferred term, and, for the APTS, by intensity and by causality (*probably* and *possibly related* to treatment). All adverse events, adverse events leading to withdrawal, and SAEs were included in the data listings.
- Absolute values and changes from randomisation by visit and to the last assessment in clinical safety laboratory tests, vital signs, and ECG parameter values were summarised for the APTS and weight/BMI were summarised for the APTSPA and APTS, all using descriptive techniques. Post-randomisation potentially clinically significant (PCS) values were flagged and tabulated for the APTS. The PCS criteria for clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters are presented in Table 1.
- In addition to the PCS criteria for liver tests, the following criteria were used to assess signals for potential liver injury; these values were flagged and summarised for patients in the APTS fulfilling these criteria at any single post-baseline visit:
  - aspartate aminotransferase or alanine aminotransferase value ≥3 times the upper limit of normal (ULN) or ≥3 times the baseline value AND
  - total bilirubin value ≥2 times ULN or ≥2 times the baseline value
- The results of urinalysis were tabulated (dipsticks) and listed (microscopy) for the APTS (Period B).
- The results of the physical examinations were summarised for the APTS (Period B).
- The number and percentages of patients with post-randomisation suicidality-related events, based on the eC-SSRS data, were summarised for the APTS (Period B). In addition, the worst case per evaluation of the eC-SSRS was mapped into the C-CASA categories (Table 2). The number and percentage of patients in the C-CASA categories were summarised for all post-randomisation assessment time points during Period B.
- The absolute value and change from randomisation in AIMS total score, BARS Global Clinical Assessment of Akathisia score, and mSAS total score were summarised for the APTS (Period B).

Patient Disposition and Analysis Sets

- The randomisation list, including patient identifier and treatment assigned, are in Listing 1.
- Patient disposition for the APTS (Period B) by site is summarised in Table 3 and by country in Table 4. The number of patients in the analyses sets are summarised in Table 5.
- A total of 417 patients were enrolled in the study and of these 413 patients were included in the APTSPA and entered Period A. A total of 145 patients (35.1%) completed Periods B or A+ and 268 patients (64.9%) were withdrawn from the study during Periods A, B or A+ (Tables 6 and 7). The primary reason for withdrawal during the study was administrative or other reason(s) and of the 268 patients who withdrew from the study 117 withdrew due to the early termination of the study (Tables 7 and 8).
- Patient disposition in Period A is summarised below (all patients received paroxetine/sertraline and adjunctive placebo):

	Total	
	n	(%)
Patients enrolled	417	
Patients treated in Period A (APTSPA):	413	
Patients completed Period A	231	(55.9)
Patients withdrawn in Period A	182	(44.1)
Primary reason for withdrawal in Period A:		
Adverse event(s)	24	(5.8)
Lack of efficacy	4	(1.0)
Non-compliance with IMP	6	(1.5)
Protocol violation	12	(2.9)
Withdrawal of consent	21	(5.1)
Lost to follow-up	40	(9.7)
Administrative or other reason(s)	75	(18.2)

Cross-references: Tables 5 and 9.

- Patient disposition in Period B is summarised below:

	Placebo + PAR/SER		Brex + PAR/SER		Total	
	n	(%)	n	(%)	n	(%)
Patients treated in Period B (APTS):	17		23		40	
Patients completed Period B	12	(70.6)	14	(60.9)	26	(65.0)
Patients withdrawn in Period B	5	(29.4)	9	(39.1)	14	(35.0)
Primary reason for withdrawal in Period B						
Adverse event(s)	0		1	(4.3)	1	(2.5)
Withdrawal of consent	0		1	(4.3)	1	(2.5)
Administrative or other reason(s)	5	(29.4)	7	(30.4)	12	(30.0)
Full-analysis Set (FAS)	17		23		40	

Cross-references: Tables 5, 10, and 11.

Patient Disposition and Analysis Sets (continued)

- Patient disposition in Period A+ is summarised below (all patients received paroxetine/sertraline and adjunctive placebo):

	Total	
	n	(%)
Patients treated in Period A+ (APTSPA+):	190	
Patients completed Period A+	119	(62.6)
Patients withdrawn in Period A+	71	(37.4)
Primary reason for withdrawal in Period A+		
Adverse event(s)	7	(3.7)
Non-compliance with IMP	1	(0.5)
Protocol violation	6	(3.2)
Withdrawal of consent	9	(4.7)
Lost to follow-up	5	(2.6)
Administrative or other reason(s)	43	(22.6)

Cross-references: Tables 12 and 13.

- Withdrawals by all reasons are summarised in Tables 14 (withdrawals during Periods A, B, or A+), 15 (withdrawals during Period A), 16 (withdrawals during Period B), and 17 (withdrawals during Period A+). All withdrawals are in Listing 2.

Demography of Study Population

- The mean age of the patients in the APTSPA was 41 years, 75% of the patients were White and approximately one-third were men (Table 18). The overall mean baseline weight, BMI, and waist circumference were 82 kg, 28.5 kg/m^2, and 94 cm, respectively (Table 19).
- The mean age of the patients in the APTS was 46 years, 80% the patients were White and approximately half were men (Table 20). The overall mean baseline weight, BMI, and waist circumference were 85 kg, 29 kg/m^2, and 97 cm (Table 21).
- The demography of the patients in the APTSPA+ was similar to that of the patients in the APTSPA (Table 22).
- The PTSD history at screening is summarised in Table 23 for patients in the APTSPA and in Table 24 for patients in the APTS. For the patients in the APTSPA or APTS, mean time since trauma leading to PTSD was approximately 5.2 years (range: 0 to 15), mean time since onset of PTSD was approximately 4.7 years (range: 0 to 15), and mean time since diagnosis was approximately 2 years (range: 0 to 15).
- The primary event leading to PTSD is summarised in Table 25 for patients in the APTSPA and in Table 26 for patients in the APTS. The most common primary events leading to PTSD were physical assault and assault with a weapon.
- Patients exposed to a war zone could have been there as a civilian or as a combatant, and are summarised in Table 27 for patients in the APTSPA and in Table 28 for patients in the APTS. Of the 413 patients in the APTSPA, 81 were exposed to a war zone and the majority of these were exposed as a combatant (62 patients out of 81).
- Prior PTSD treatment is summarised in Table 29 for patients in the APTSPA and in Table 30 for patients in the APTS. Only 30% of the patients were previously treated with paroxetine or sertraline although they are the only two treatments currently approved for PTSD.
- A total of 411 out of the 413 patients in the APTSPA were also diagnosed with PTSD according to DSM-5 criteria (Table 31).
- The baseline rating scale scores (Visit 2) for the patients in the APTSPA are summarised in Table 32 and in Table 33 for the patients in the APTS. The patients in the APTSPA had a mean CAPS-2 total score of 89 indicating that the patients had severe to extreme symptomatology and a mean CGI-S score of 4.9 indicating that they were markedly ill. The mean MADRS total score was 22 indicating that many patients had depressive symptoms of at least mild to moderate severity. The mean SDS mean score was 7 indicating some level of functional impairment. The patients in the APTS had a mean CAPS-2 total score of 83, a mean CGI-S score of 4.4, a mean MADRS total score of 21, and a mean SDS mean score of 7 at baseline.
- The medical, neurological, and psychiatric disorders (ongoing and not ongoing at baseline) in patients in the APTSPA and APTS are presented in Tables 34 to 37. The concurrent (ongoing at baseline) medical, neurological, and psychiatric disorders that were present in >2 patients in either of the treatment groups in the APTS were *obesity*, *back pain*, *insomnia*, *hypertension*, and *asthma* (Table 37).
- Alcohol consumption and smoking habits for patients in the APTSPA and APTS are presented in Tables 38 to 41.
- The physical examinations at screening for the patients in the APTS are summarised in Table 42.
- For patients in the APTS, concomitant medication stopped before first dose of randomised IMP, continued after first dose of randomised IMP, and started at or after first dose of randomised IMP are presented in Tables 43, 44, and 45, respectively.

Exposure

- The average modal and mean doses of brexpiprazole were 1.91 mg and 1.80 mg, respectively (Table 46). The median exposure to IMP for the APTS (Period B) was 108 days (brexpiprazole + paroxetine/sertraline; hereafter referred to as brexpiprazole) and 110 days (placebo + paroxetine/sertraline; hereafter referred to as placebo) (Table 47). All patients were more than 80% compliant, except 1 patient (and 1 patient with unknown compliance) (Table 48); compliance with IMP by visit for the APTS (Period B) is summarised in Table 49. The average modal and mean doses to paroxetine and sertraline for the APTSPA (Period A) and APTS (Period B) are summarised in Tables 50 and 51, respectively. Exposure to paroxetine and sertraline for the APTSPA (Period A), APTS (Period B), and APTSPA+ (Period A+) are summarised in Tables 52, 53 and 54, respectively.

Efficacy Results

- The limited number of randomised patients resulted in insufficient data for any meaningful analyses.
- Absolute values by visit for the ATPSPA (Period A) for the CAPS-2 and CGI-S are presented in Tables 55 and 56, respectively.
- Absolute values by visit for the FAS (Period B) for the CAPS-2 and CGI-S are presented by treatment group in Tables 57 and 58, respectively.

Pharmakokinetic Results

- The limited number of randomised patients resulted in insufficient data for any meaningful analyses.

Safety Results

- Adverse events are presented for all periods. The focus of this safety presentation is, however, the comparison of brexpiprazole *versus* placebo during double-blind treatment for the APTS (Period B). The adverse event data for the APTS in Period B are therefore presented before adverse event data for the APTSPA in Period A and the APTSPA+ in Period A+. Furthermore, clinical safety laboratory values, vital signs, and ECGs are only presented for the APTS (Period B) while weight is presented for the APTS (Period B) and the APTSPA (Period A).

Adverse Events

- All adverse events are in Listing 3 and all serious adverse events (SAEs) are in Listing 4. All TEAEs leading to withdrawal for the APTS in Period B are in Listing 5.
- Pre-treatment adverse events are summarised by SOC and preferred term in Table 59.
- The incidence of TEAEs for the APTS during Period B is summarised below:

	Placebo + PAR/SER		Brex + PAR/SER	
	n	(%)	n	(%)
Patients treated	17		23	
Patients who died	0	(0.0)	0	(0.0)
Patients with serious AEs (SAEs)	0	(0.0)	0	(0.0)
Patients with AEs leading to withdrawal	0	(0.0)	1	(4.3)
Patients with TEAEs	8	(47.1)	6	(26.1)
Total number of TEAEs	11		12	

Cross-reference: Table 60

- For the APTS, no patients died or had treatment-emergent SAEs.
- TEAEs are summarised by system organ class (SOC) and preferred term in Table 61 and by preferred term in Table 62. All TEAEs were reported in 1 patient only in any treatment group, except *accidental overdose* (2 patients, brexpiprazole group). Two of the 11 adverse events in the placebo group and 3 of the 12 adverse events in the brexpiprazole group were *possibly* or *probably related* to treatment (Table 63). All TEAEs were *mild* or *moderate* (Table 64 and Listing 3).
- Two of the 12 adverse events in the brexpiprazole group were extrapyramidal symptoms (EPS)-related TEAEs (*muscle spasms* and *tremor*) (Table 65 and Listing 3). None of the patients in the placebo group had any EPS-related TEAEs.
- For the APTS, 1 patient in the brexpiprazole group withdrew due to an adverse event (*intentional self-injury*) (Table 66 and Listing 5). None of the patients in the placebo group withdrew due to adverse events.

Safety Results (continued)

- The adverse event incidence for the APTSPA during Period A is summarised below:

	Total	
	n	(%)
Patients treated	413	
Patients who died	0	(0.0)
Patients with serious AEs (SAEs)	3	(0.7)
Patients with AEs leading to withdrawal	31	(7.5)
Patients with AEs	281	(68.0)
Total number of AEs	783	

Cross-reference: Table 67

- No patients in the APTSPA died.
- Three patients in the APTSPA had an SAE in Period A (*bronchopneumonia*, *suicidal ideation*, and *intentional self-injury*) (Table 68 and Listing 4).
- The adverse events in the APTSPA in Period A are summarised by SOC and preferred term in Table 69, by SOC, preferred term, and paroxetine/sertraline in Table 70, and by preferred term in Table 71. Overall, the four adverse events with the highest incidence were *nausea* (13.8%), *headache* (10.9%), *diarrhoea* (8.2%), and *somnolence* (7.3%).
- For the APTSPA, 31 patients (7.5%) withdrew due to adverse events. The adverse events leading to withdrawal are summarised by SOC and preferred term in Table 72 and by preferred term in Table 73. For 20 of the 31 patients, the adverse events leading to withdrawal were *possibly* or *probably related* to treatment (Listing 6).
- The adverse event incidence for the APTSPA+ during Period A+ is summarised below:

	Total	
	n	(%)
Patients treated	190	
Patients who died	0	(0.0)
Patients with serious AEs (SAEs)	4	(2.1)
Patients with AEs leading to withdrawal	6	(3.2)
Patients with AEs	84	(44.2)
Total number of AEs	172	

Cross-reference: Table 74

- No patients in the APTSPA+ died.
- Four patients in the APTSPA+ had an SAE in Period A+ (*pulmonary embolism*, *rectal adenocarcinoma, suicide attempt, and head injury*) (Table 75 and Listing 4).
- For the APTSPA+, the adverse events in Period A+ are summarised by system organ class (SOC) and preferred term in Table 76 and by preferred term in Table 77. Overall, the four adverse events with the highest incidence were *diarrhoea* (4.7%), *weight increased* (3.7%), *nausea* (3.2%), and *upper respiratory tract infection* (2.6%).
- For the APTSPA+, 6 patients withdrew due to adverse events. The adverse events leading to withdrawal are summarised by SOC and preferred term in Table 78. For 2 of the 6 patients, the adverse events leading to withdrawal were *possibly* or *probably related* to treatment (Listing 7).

Safety Results (continued)

Clinical Safety Laboratory Parameters

- The clinical safety laboratory values in the APTS (Period B) are summarised in Tables 79 (cardiac/skeletal muscle), 80 (electrolytes), 81 (endocrine/metabolic), 82 (haematology), 83 (kidney), 84 (fasting lipids), and 85 (liver). The changes from randomisation in clinical safety laboratory values are summarised in Tables 86 (cardiac/skeletal muscle), 87 (electrolytes), 88 (endocrine/metabolic), 89 (haematology), 90 (kidney), 91 (fasting lipids), and 92 (liver). An overview of the reference ranges and the PCS criteria is in Table 1. There were no clinically relevant findings.
- The post-randomisation PCS clinical safety laboratory values are summarised in Tables 93 (cardiac/skeletal muscle), 94 (electrolytes), 95 (endocrine/metabolic), 96 (haematology), 97 (kidney), 98 (fasting lipids), and 99 (liver). All PCS clinical safety laboratory values are in Listing 8 and all adverse events in patients with a PCS clinical safety laboratory value are in Listing 9.
- In the APTS (Period B), PCS high values (reported by >5 patients) were seen for glucose (9 patients, 6 of whom were treated with brexpiprazole), cholesterol (12 patients; 7 of whom were treated with brexpiprazole), low density lipoprotein (LDL) cholesterol (12 patients, 7 of whom were treated with brexpiprazole), and triglycerides (15 patients; 8 of whom were treated with brexpiprazole), and PCS low values (reported by >5 patients) were seen for high density lipoprotein (HDL) cholesterol (7 patients, 2 of whom were treated with brexpiprazole).
- One patient in the APTS treated with placebo had PCS high cholesterol, LDL cholesterol, triglycerides and PCS low HDL cholesterol at Screening and multiple visits during Periods A and B and reported *hypercholesterolaemia* during Period B. No other patients reported adverse events associated with any of the PCS clinical safety laboratory values (Listing 9).
- None of the patients met the criteria for potential liver injury.
- The urinalysis parameters are summarised in Table 100 and the microscopy results are in Listing 10. The majority of the results were *negative*.

ECGs

- The ECG parameter values in the APTS (Period B) and the changes from randomisation therein are summarised in Tables 101 and 102, respectively. There were no clinically relevant findings. None of the patients in either treatment group had PCS ECG parameter values (Table 103; for an overview of the reference ranges and the PCS criteria, see Table 1).

Vital Signs

- The vital signs in the APTS (Period B) and the changes from randomisation therein are summarised in Tables 104 and 105, respectively. There were no clinically relevant findings. None of the patients in either treatment group had PCS vital signs (Table 106; for an overview of the reference ranges and the PCS criteria, see Table 1).

Safety Results (continued)

Weight, BMI, and Waist Circumference

- The weight, BMI, and waist circumference in the APTS (Period B) and the changes from randomisation therein are summarised in Tables 107 and 108, respectively. Patients treated with placebo had a mean weight increase of 0.4 kg from randomisation to Week 16 while patients treated with brexpiprazole had a mean weight increase of 2.4 kg. Three patients treated with brexpiprazole had a PCS weight increase (Table 109). There were no adverse events associated with any of the PCS weight increases (Listings 11 and 12). For an overview of the reference ranges and the PCS criteria, see Table 1.
- The weight, BMI, and waist circumference in the APTSPA (Period A) and the changes from baseline in are summarised therein in Tables 110 and 111, respectively. There was no clinically relevant mean change in weight during Period A (-0.1 kg). Eleven patients had a PCS weight decrease and 12 patients had a PCS weight increase (Table 112).

Physical Examination

- The results of the physical examinations in the APTS (Period B) are summarised in Table 113 and the majority of the results were *normal*.

eC-SSRS

- In the APTS (Period B), 2 patients in the brexpiprazole group had suicidal ideation (1 *wish to be dead* and 1 *active suicidal ideation with any methods [no plan] without intent to act*); 1 patient in the placebo group had suicidal ideation (*wish to be dead*) (Tables 114 and 115 and Listing 13). None of the events were reported as SAEs and no other SAEs related to suicidality were reported.

Extrapyramidal Symptoms Rating Scales (AIMS, BARS, and mSAS)

- The AIMS total scores and the changes from randomisation for the APTS (Period B) are summarised in Tables 116 and 117, respectively. The BARS global clinical assessment of akathisia scores and the changes from randomisation for the APTS (Period B) are summarised in Tables 118 and 119, respectively. The mSAS total scores and the changes from randomisation for the APTS (Period B) are summarised in Tables 120 and 121, respectively.
- There were no clinically relevant changes in extrapyramidal symptom scores in the APTS (Period B) based on the results of the AIMS, BARS, and mSAS ratings.

Conclusions

- Due to the low number of randomised patients, no firm conclusions can be drawn regarding safety; however, the data indicate that the patients who were treated with brexpiprazole adjunctive to paroxetine or sertraline tolerated the drug well.
- No conclusions regarding efficacy could be drawn.

Report Date

5 April 2016

This study was conducted in compliance with the principles of *Good Clinical Practice*.